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☐ 1. Document ID: JP 2002525367 W WO 200018759 A1 AU 9961059 A EP 1117657 A1
US 20020028812 A1 US 6348463 B1

L1: Entry 1 of 1

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Aug 13, 2002

DERWENT-ACC-NO: 2000-293092

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TITLE: New substituted phenyl derivatives are selective inhibitors of alpha4 integrin inhibitors used to treat inflammatory disorders involving extravasation of leukocytes e.g. rheumatoid arthritis, multiple sclerosis and allograft rejection

INVENTOR: ARCHIBALD, S C; HEAD, J C ; HUTCHINSON, B W ; PORTER, J R ; WARRELOW, G J

PRIORITY-DATA: 1998GB-0021061 (September 28, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2002525367 W	August 13, 2002		116	C07D401/12
WO 200018759 A1	April 6, 2000	E	094	C07D401/12
AU 9961059 A	April 17, 2000		000	C07D401/12
EP 1117657 A1	July 25, 2001	E	000	C07D401/12
US 20020028812 A1	March 7, 2002		000	A61K031/497
US 6348463 B1	February 19, 2002		000	C07D239/24

INT-CL (IPC): A61 K 31/195; A61 K 31/44; A61 K 31/4409; A61 K 31/4436; A61 K 31/444; A61 K 31/4709; A61 K 31/497; A61 K 31/498; A61 K 31/501; A61 K 31/505; A61 K 31/506; A61 K 31/53; A61 K 31/5377; A61 P 1/00; A61 P 3/10; A61 P 11/06; A61 P 17/00; A61 P 17/06; A61 P 19/02; A61 P 25/00; A61 P 29/00; A61 P 37/02; A61 P 43/00; C07 D 213/02; C07 D 213/81; C07 D 215/38; C07 D 239/24; C07 D 251/46; C07 D 401/12; C07 D 401/14; C07 D 409/12; C07 D 413/12

ABSTRACTED-PUB-NO: US 6348463B

BASIC-ABSTRACT:

NOVELTY - Substituted phenyl derivatives (I), their salts, solvates, hydrates and N-oxides are new.

DETAILED DESCRIPTION - Substituted phenyl derivatives of formula (I), their salts, solvates, hydrates and N-oxides are new.

Ar1 = aromatic or heteroaromatic group;

R1 - R5 = L2(Alk3)tL3(R7)u;

L2, L3 = covalent bond or linker atom or group;

t = 0 or 1;

u = 1 - 3;

Alk3 = aliphatic or heteroaliphatic chain;

R7 = H, halogen, alkyl, XR8, NR8R9, NO2, CN, CO2R8, SO3H, SO2R8, OCO2R8, C(X)NR8R9, OCONR8R9, COR8, OCOR8, NR8C(X)R9, SO2NR8R9, NR8SO2R9 or NR8C(X)NR9R10;

R8 - R10 = H or optionally substituted alkyl;

X = O or S;

Alk1 = optionally substituted aliphatic or heteroaliphatic chain;

L1 = covalent bond or linker atom or group;

Alk2 = straight or branched alkylene;

m, r, g = 0 or 1;

R6, Ra = H or methyl;

R = CO2H or derivative; and

Ar2 = optionally substituted aromatic or heteroaromatic group.

An INDEPENDENT CLAIM is also provided for a composition comprising (I).

ACTIVITY - Antiinflammatory; antirheumatic; antiarthritic; vasotropic; dermatological; neuroprotective; immunosuppressive; antidiabetic; antipsoriatic; gastrointestinal.

MECHANISM OF ACTION - Integrin- alpha 4 antagonist.

NUNC plates were coated with goat anti-human IgG Fc gamma specific antibody, washed with PBS and blocked with PBS/BSA. The plates were washed again and 2d VCAM-Ig in PBS/BSA added and the plates incubated at room temperature for 60 minutes on a rocking platform. The plates were washed and incubated with compounds of the invention and Jurkat cells for 30 minutes at 37 deg. C. The plates were washed, fixed with methanol and stained with Rose Bengal before measuring absorbance. (I) showed IC50 of at most 1 micro M, compared with IC50 of at least 50 micro M for non-alpha 4 integrins.

USE - For treatment of inflammatory disorders where extravasation of leukocytes is involved, such as rheumatoid arthritis, vasculitis, polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses (e.g. psoriasis or dermatitis) and inflammatory bowel disease.

ADVANTAGE - Potent and selective inhibitors of alpha 4 integrins.

ABSTRACTED-PUB-NO:

US20020028812A EQUIVALENT-ABSTRACTS:

NOVELTY - Substituted phenyl derivatives (I), their salts, solvates, hydrates and N-oxides are new.

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L2, L3 = covalent bond or linker atom or group;

t = 0 or 1;

u = 1 - 3;

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R7 = H, halogen, alkyl, XR8, NR8R9, NO2, CN, CO2R8, SO3H, SO2R8, OCO2R8, C(X)NR8R9, OCONR8R9, COR8, OCOR8, NR8C(X)R9, SO2NR8R9, NR8SO2R9 or NR8C(X)NR9R10;

R8 - R10 = H or optionally substituted alkyl;

X = O or S;

Alk1 = optionally substituted aliphatic or heteroaliphatic chain;

L1 = covalent bond or linker atom or group;

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m, r, g = 0 or 1;

R6, Ra = H or methyl;

R = CO2H or derivative; and

Ar2 = optionally substituted aromatic or heteroaromatic group.

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R8 - R10 = H or optionally substituted alkyl;

X = O or S;

Alk1 = optionally substituted aliphatic or heteroaliphatic chain;

L1 = covalent bond or linker atom or group;

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WO 200018759A

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